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(54) Title: PIPERAZINE COMPOUNDS AND THEIR PHAMACEUTICAL USE

(57) Abstract: This invention relates to piperazine derivatives and their use as pharmaceuticals.

PIPERAZINE COMPOUNDS AND THEIR PHARMACEUTICAL USE

This invention relates to piperazine derivatives and their use as pharmaceuticals.

Many medically significant biological processes are mediated by proteins participating in signal transduction pathways that involve G-proteins and/or second messengers.

Polypeptides and polynucleotides encoding the human 7-transmembrane G-protein coupled neuropeptide receptor, orexin-1 (HFGAN72), have been identified and are disclosed in EP-A-875565, EP-A-875566 and WO 96/34877. Polypeptides and polynucleotides encoding a second human orexin receptor, orexin-2 (HFGANP), have been identified and are disclosed in EP-A-893498.

Polypeptides and polynucleotides encoding polypeptides which are ligands for the orexin-1 receptor, e.g. orexin-A (Lig72A) are disclosed in EP-A-849361.

Orexin receptors are found in the mammalian host and may be responsible for many biological functions, including pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Gilles de la Tourett's syndrome; disturbed biological and circadian rhythms; feeding disorders, such as anorexia, bulimia, cachexia, and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome / disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor / adenoma; hypothalamic diseases; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; dwarfism; gigantism; acromegaly; sleep disturbances associated with such diseases as neurological disorders, neuropathic pain and restless leg syndrome, heart and lung diseases; acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardial infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; head injury such as sub-arachnoid haemorrhage associated with traumatic head injury; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain, such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection, e.g. HIV, post-polio syndrome, and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain;

post-stroke pain; post-operative pain; neuralgia; nausea, vomiting; conditions associated with visceral pain including irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegenerative disorders, which includes nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration, epilepsy, and seizure disorders.

Experiments have shown that central administration of the ligand orexin-A (described in more detail below) stimulated food intake in freely-feeding rats during a 4 hour time period. This increase was approximately four-fold over control rats receiving vehicle. These data suggest that orexin-A may be an endogenous regulator of appetite. Therefore, antagonists of its receptor may be useful in the treatment of obesity and diabetes, see *Cell*, 1998, **92**, 573-585.

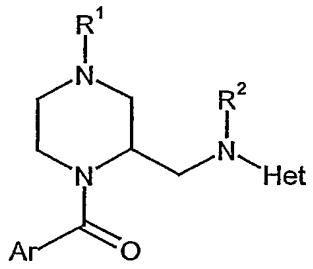
There is a significant incidence of obesity in westernised societies. According to WHO definitions a mean of 35% of subjects in 39 studies were overweight and a further 22% clinically obese. It has been estimated that 5.7% of all healthcare costs in the USA are a consequence of obesity. About 85% of Type 2 diabetics are obese, and diet and exercise are of value in all diabetics. The incidence of diagnosed diabetes in westernised countries is typically 5% and there are estimated to be an equal number undiagnosed. The incidence of both diseases is rising, demonstrating the inadequacy of current treatments which may be either ineffective or have toxicity risks including cardiovascular effects. Treatment of diabetes with sulfonylureas or insulin can cause hypoglycaemia, whilst metformin causes GI side-effects. No drug treatment for Type 2 diabetes has been shown to reduce the long-term complications of the disease. Insulin sensitisers will be useful for many diabetics, however they do not have an anti-obesity effect.

Rat sleep/EEG studies have also shown that central administration of orexin-A, an agonist of the orexin receptors, causes a dose-related increase in arousal, largely at the expense of a reduction in paradoxical sleep and slow wave sleep 2, when administered at the onset of the normal sleep period. Therefore antagonists of its receptor may be useful in the treatment of sleep disorders including insomnia.

The present invention provides piperazine derivatives which are non-peptide antagonists of human orexin receptors, in particular orexin-1 receptors. In particular, these compounds are of potential use in the treatment of obesity, including obesity observed in Type 2 (non-insulin-dependent) diabetes patients, and/or sleep disorders, and/or stroke, particularly ischemic or haemorrhagic stroke, and/or for blocking the emetic response i.e. useful in the treatment of nausea and vomiting.

International Patent Applications WO99/09024, WO99/58533, WO00/47577, and WO00/47580, disclose phenyl urea derivatives and WO00/47576, discloses quinolinyl cinnamide derivatives as orexin receptor antagonists.

According to the invention there is provided compounds of formula (I):



(I)

wherein:

R^1 and R^2 independently represent hydrogen or optionally substituted (C_{1-6})alkyl;

Het represents an optionally substituted 5- or 6- membered heteroaryl group containing up to 3 heteroatoms selected from N, O, and S, or an optionally substituted bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

Ar represents a phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heteroaryl group is substituted by R^3, and further optional substituents; or Ar represents an optionally substituted bicyclic aromatic or heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^3 independently represents hydrogen, an optionally substituted (C_{1-4})alkoxy, halo, optionally substituted (C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 3 heteroatoms selected from N, O and S;

or pharmaceutically acceptable derivatives thereof.

Examples of 5- or 6- membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, or pyrazolyl.

When Het represents a bicyclic heteroaryl it may be selected from isoquinolinyl, quinoxalinyl, benzoxazolyl, quinolinyl, napththyridinyl, benzofuranyl, benzimidazolyl, benzothienyl, indolyl, benzothiazoyl, quinazolinyl or benzoxazolyl.

Examples of where Ar represents an optionally substituted bicyclic aromatic or heteroaromatic include naphthyl, quinolinyl, napththyridinyl, benzofuranyl, benzimidazolyl, isoquinolinyl, quinoxalinyl, quinazolinyl or benzoxazolyl.

Preferably R^1 is hydrogen or methyl.

Preferably R^2 is hydrogen or methyl.

Preferably Het represents pyridyl, pyrimidinyl or quinoxalinyl.

Preferably when Ar represents phenyl, or a 5-or 6- membered heteroaryl group the substituent R^3 is *ortho* to the amide carbonyl group.

Preferably Ar represents optionally substituted thiazolyl or pyrazolyl.

Examples of groups where R^3 is a 5- or 6-membered heterocyclic ring containing up to 3 heteroatoms selected from N, O and S, include furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl,

imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, piperazine, triazinyl, pyridazyl, pyrimidinyl, isothiazolyl, isoxazolyl, pyrazinyl, pyrazolyl, piperidine, thiomorpholine and morpholine.

Preferably R^3 represents trifluoromethoxy, methoxy, ethoxy, halo, or optionally substituted phenyl, pyridyl, pyrazolyl, pyrimidinyl or oxadiazolyl group.

Even more preferably R^3 represents an optionally substituted phenyl, e.g. 4-fluorophenyl.

When used herein the term amide carbonyl group means the -C(O)-N- bond wherein the N forms part of the piperazine ring.

Optional substituents for the groups R^1 to R^3, Ar and Het include halogen, hydroxy, oxo, cyano, nitro, (C_{1-4})alkyl, (C_{1-4})alkoxy, halo(C_{1-4})alkyl, halo(C_{1-4})alkoxy, (C_{1-4})acyl, aryl, aryl(C_{1-4})alkyl, aryl(C_{1-4})alkoxy, (C_{1-4})alkylthio, (C_{1-4})alkylamino(C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, hydroxy(C_{1-4})alkoxy, (C_{1-4})alkoxy(C_{1-4})alkyl, (C_{3-6})cycloalkyl(C_{1-4})alkoxy, (C_{1-4})alkanoyl, (C_{1-4})alkoxycarbonyl, (C_{1-4})alkylsulfonyl, (C_{1-4})alkylsulfonyloxy, (C_{1-4})alkylsulfonyl(C_{1-4})alkyl, arylsulfonyl, arylsulfonyloxy, arylsulfonyl(C_{1-4})alkyl, (C_{1-4})alkylsulfonamido, (C_{1-4})alkylamido, (C_{1-4})alkylsulfonamido(C_{1-4})alkyl, (C_{1-4})alkylamido(C_{1-4})alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamido(C_{1-4})alkyl, arylcarboxamido(C_{1-4})alkyl, aroyl, aroyl(C_{1-4})alkyl, or aryl(C_{1-4})alkanoyl group; a group R^aR^bN-, $R^aR^bN(CH_2)n$-, $R^aR^bN(CH_2)nO$-, $R^aOCO(CH_2)_r$, $R^aCON(R^b)(CH_2)_r$, $R^aR^bNCO(CH_2)_r$, $R^aR^bNSO_2(CH_2)_r$ or $R^aSO_2NR^b(CH_2)_r$ where each of R^a and R^b independently represents a hydrogen atom or a (C_{1-4})alkyl group or where appropriate R^aR^b forms part of a (C_{3-6})azacycloalkane or (C_{3-6})(2-oxo)azacycloalkane ring, n represents an interger from 1 to 4, and r represents zero or an integer from 1 to 4. Additionally when the substituent is $R^aR^bN(CH_2)n$- or $R^aR^bN(CH_2)nO$, R^a with at least one CH_2 of the $(CH_2)n$ portion of the group form a (C_{3-6})azacycloalkane and R^b represents hydrogen, a (C_{1-4})alkyl group or with the nitrogen to which it is attached forms a second (C_{3-6})azacycloalkane fused to the first (C_{3-6})azacycloalkane.

Preferred optional substituents for Ar are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl or (C_{1-4})alkoxy(C_{1-4})alkyl.

Preferred optional substituents for Het are halogen, cyano, (C_{1-4})alkyl, hydroxy(C_{1-4})alkyl, (C_{1-4})acyl, (C_{1-4})alkoxy(C_{1-4})alkyl or $R^aR^bNCO(CH_2)_r$.

Preferred optional substituents for R^3 are halogen or (C_{1-4})alkoxy(C_{1-4})alkyl.

In addition Het may be optionally substituted by a phenyl ring optionally substituted by a halogen, cyano, or C_{1-4}alkanoyl or C_{1-4}alkylsulfonyl group; or by a 5- or 6-membered heterocyclic ring, optionally substituted by a (C_{1-2})alkyl or R^aR^bN- group; wherein R^a and R^b are as defined above.

When used herein the term aryl means a 5- to 6- membered aromatic ring for example phenyl, or a 7 to 12 membered bicyclic ring system where at least one of the rings is aromatic for example naphthyl.

In the groups Ar and Het, substituents positioned *ortho* to one another may be linked to form a fused ring.

When a halogen atom is present in the compound of formula (I) it may be fluorine, chlorine, bromine or iodine.

When the compound of formula (I) contains an alkyl group, whether alone or forming part of a larger group, e.g. alkoxy or alkylthio, the alkyl group may be straight chain, branched or cyclic, or combinations thereof, it is preferably methyl or ethyl.

It will be appreciated that compounds of formula (I) may exist as *R* or *S* enantiomers. The present invention includes within its scope all such isomers, including mixtures. Where additional chiral centres are present in compounds of formula (I), the present invention includes within its scope all possible diastereoismers, including mixtures thereof. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

It will be understood that the invention includes pharmaceutically acceptable derivatives of compounds of formula (I) and that these are included within the scope of the invention.

Particular compounds according to the invention include those mentioned in the examples and their pharmaceutically acceptable derivatives.

As used herein "pharmaceutically acceptable derivative" includes any pharmaceutically acceptable salt, ester or salt of such ester of a compound of formula (I) which, upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolic or residue thereof.

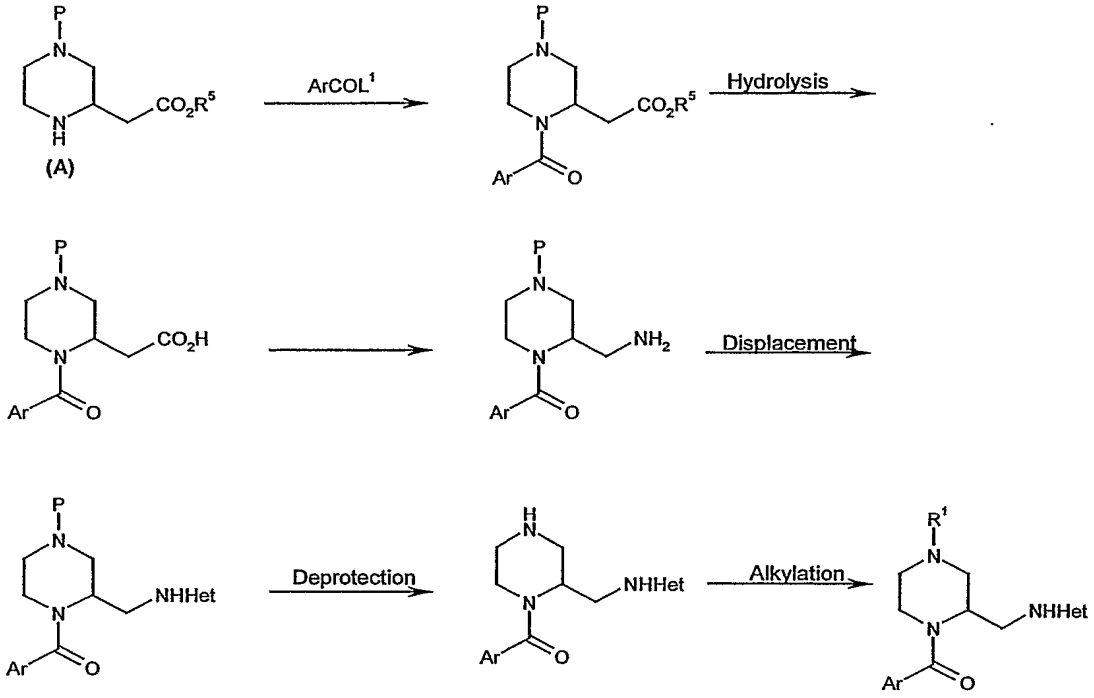
It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulphuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other salts e.g. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

Since the compounds of formula (I) are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions.

According to a further feature of the invention there is provided a process for the preparation of compounds of formula (I) and salts thereof. The following schemes detail synthetic routes to compounds of the invention.

Scheme 1



wherein Ar, R^1, Het are as defined for formula (I), R^5 is an optionally substituted C_{1-6} alkyl group, P is a protecting group and L^1 is a leaving group.

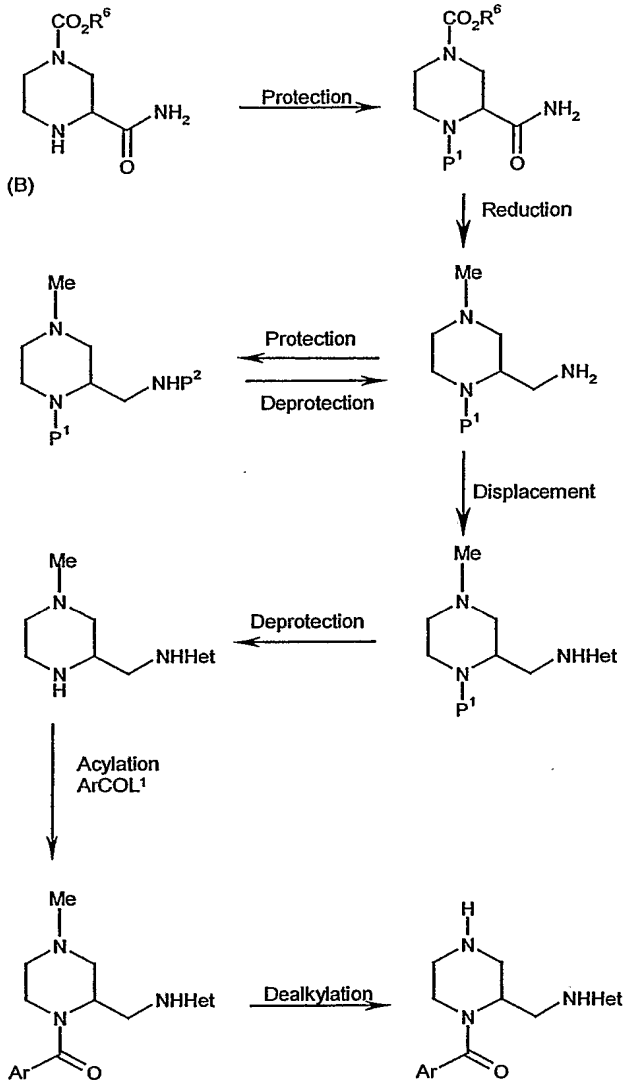
Examples of protecting groups P include *t*-butyloxycarbonyl, trifluoroacetyl, benzyloxycarbonyl and optionally substituted benzyl. Deprotection conditions will depend on the particular protecting group; for the groups mentioned above these are respectively, acid (e.g. trifluoroacetic acid in dichloromethane), base (e.g. potassium carbonate in a solvent such as aqueous methanol) and catalytic hydrogenolysis in an inert solvent (e.g. using palladium on charcoal in a lower alcohol or ethyl acetate).

Examples of suitable leaving groups L^1 include halogen, hydroxy, OC(=O)alkyl OC(=O)O-alkyl and OSO_2Me. Acylation may be carried out using a wide range of known conditions, e.g. in an inert solvent such as dichloromethane, in the presence of a base such as triethylamine. Alternatively these steps may be carried out when L^1 represents hydroxy, in which case the reaction takes place in an inert solvent such as dichloromethane in the presence of a diimide reagent such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and an activator such as 1-hydroxybenzotriazole.

Within the scheme there is scope for functional group interconversion and interchange of protecting group.

Compound A can be prepared by known methods, e.g. WO 9631505.

Scheme 2



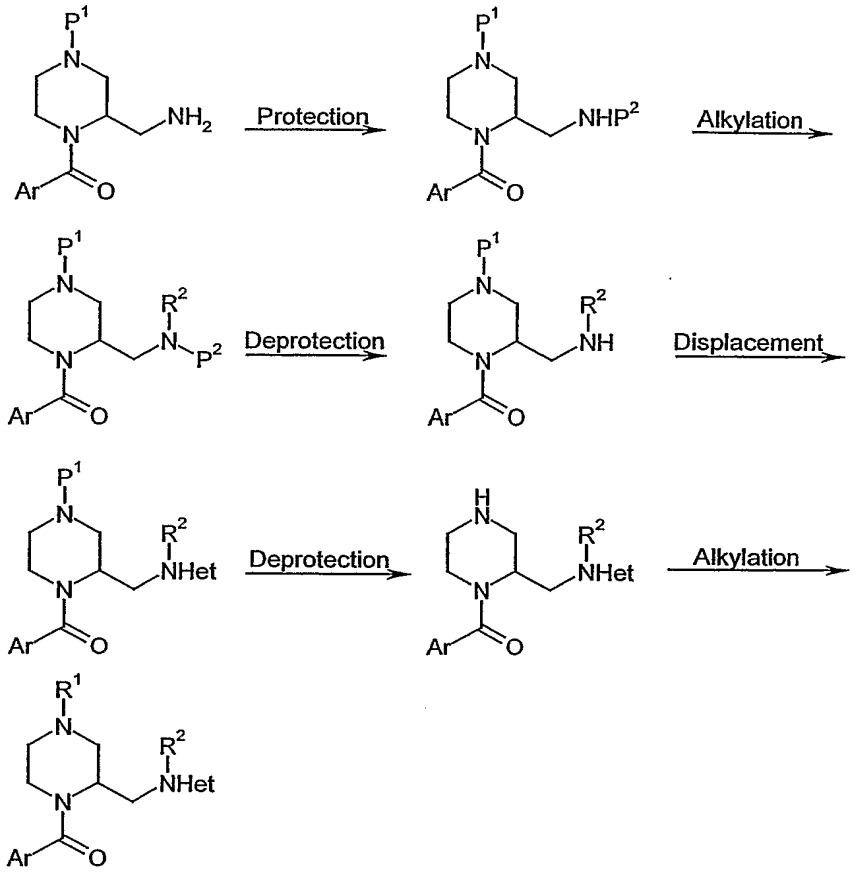
wherein Ar, Het are as defined for formula (1), R^6 is an optionally substituted C_{1-6} alkyl group, and P^1 and P^2 are protecting groups and L^1 is a leaving group as described for scheme 1.

Reduction of the amide can be carried out using known methods e.g. with a metal hydride reducing agent such as lithium aluminium hydride in an inert solvent such as diethyl ether or tetrahydrofuran.

Within the scheme there is scope for functional group interconversion and interchange of protecting group.

Compound B can be synthesised using known methods.

Scheme 3



wherein Ar, R^1, and Het are as defined for formula (I) and R2 is optionally substituted (C_{1-6})alkyl, P^1 and P^2 are protecting groups.

The compounds of formula (I) may be prepared singly or as compound libraries comprising at least 2, e.g. 5 to 1000, preferably 10 to 100 compounds of formula (I). Compound libraries may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of formula (I), or pharmaceutically acceptable derivatives thereof.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are useful for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity and diabetes; prolactinoma; hypoprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth hormone deficiency; Cushings syndrome/disease; hypothalamic-adrenal dysfunction; dwarfism; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases; depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis/disorder; depressive neurosis/disorder; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual

dysfunction; psychosexual dysfunction; sex disorder; sexual disorder; schizophrenia; manic depression; delerium; dementia; bulimia and hypopituitarism. The compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in the treatment of stroke, particularly ischaemic or haemorrhagic stroke. Furthermore the compounds of formula (I) or pharmaceutically acceptable derivatives thereof are also useful in blocking the emetic response.

The compounds of formula (I) and their pharmaceutically acceptable derivatives are particularly useful for the treatment of obesity, including obesity associated with Type 2 diabetes, sleep disorders, stroke and blocking the emetic response for example nausea and vomiting.

Other diseases or disorders which may be treated in accordance with the invention include disturbed biological and circadian rhythms; adrenohypophysis disease; hypophysis disease; hypophysis tumor / adenoma; adrenohypophysis hypofunction; functional or psychogenic amenorrhea; adrenohypophysis hyperfunction; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndromes I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-polio syndrome and post-herpetic neuralgia; phantom limb pain; labour pain; cancer pain; post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; and tolerance to narcotics or withdrawal from narcotics.

The invention also provides a method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I), or a pharmaceutically acceptable derivative thereof.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable derivative thereof, for use in the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

The invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable derivative thereof, in the manufacture of a medicament for the treatment or prophylaxis of diseases or disorders where an antagonist of a human orexin receptor is required.

For use in therapy the compounds of the invention are usually administered as a pharmaceutical composition. The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier.

The compounds of formula (I) and their pharmaceutically acceptable derivatives may be administered by any convenient method, e.g. by oral, parenteral, buccal, sublingual, nasal, rectal or transdermal administration, and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable derivatives which are active when given orally can be formulated as liquids or solids, e.g. as syrups, suspensions, emulsions, tablets, capsules or lozenges.

A liquid formulation will generally consist of a suspension or solution of the active ingredient in a suitable liquid carrier(s) e.g. an aqueous solvent such as water, ethanol or glycerine, or a non-aqueous solvent, such as polyethylene glycol or an oil. The formulation may also contain a suspending agent, preservative, flavouring and/or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations, such as magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures, e.g. pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), e.g. aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the active ingredient in a sterile aqueous carrier or parenterally acceptable oil, e.g. polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations typically comprise a solution or fine suspension of the active ingredient in a pharmaceutically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container which can take the form of a cartridge or refill for use with an atomising device. Alternatively the sealed container may be a disposable dispensing device such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas e.g. air, or an organic propellant such as a fluorochloro-hydrocarbon or hydrofluorocarbon. Aerosol dosage forms can also take the form of pump-atomisers.

Compositions suitable for buccal or sublingual administration include tablets, lozenges and pastilles where the active ingredient is formulated with a carrier such as sugar and acacia, tragacanth, or gelatin and glycerin.

Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base such as cocoa butter.

Compositions suitable for transdermal administration include ointments, gels and patches.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

The dose of the compound of formula (I), or a pharmaceutically acceptable derivative thereof, used in the treatment or prophylaxis of the abovementioned disorders or diseases will vary in the usual way with the particular disorder or disease being treated, the weight of the subject and other similar factors. However, as a general rule, suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 500 mg. Unit doses may be administered more than once a day for example two or

three times a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months. In the case of pharmaceutically acceptable derivatives the above figures are calculated as the parent compound of formula (I).

No toxicological effects are indicated/expected when a compound of formula (I) is administered in the above mentioned dosage range.

Human orexin-A has the amino acid sequence:

pyroGlu Pro Leu Pro Asp Cys Cys Arg Gln Lys Thr Cys Ser Cys Arg Leu
1 5 10 15

Tyr Glu Leu Leu His Gly Ala Gly Asn His Ala Ala Gly Ile Leu Thr
20 25 30

Leu-NH_2

Orexin-A can be employed in screening procedures for compounds which inhibit the ligand's activation of the orexin-1 receptor.

In general, such screening procedures involve providing appropriate cells which express the orexin-1 receptor on their surface. Such cells include cells from mammals, yeast, Drosophila or *E. coli*. In particular, a polynucleotide encoding the orexin-1 receptor is used to transfect cells to express the receptor. The expressed receptor is then contacted with a test compound and an orexin-1 receptor ligand to observe inhibition of a functional response. One such screening procedure involves the use of melanophores which are transfected to express the orexin-1 receptor, as described in WO 92/01810.

Another screening procedure involves introducing RNA encoding the orexin-1 receptor into *Xenopus* oocytes to transiently express the receptor. The receptor oocytes are then contacted with a receptor ligand and a test compound, followed by detection of inhibition of a signal in the case of screening for compounds which are thought to inhibit activation of the receptor by the ligand.

Another method involves screening for compounds which inhibit activation of the receptor by determining inhibition of binding of a labelled orexin-1 receptor ligand to cells which have the receptor on their surface. This method involves transfecting a eukaryotic cell with DNA encoding the orexin-1 receptor such that the cell expresses the receptor on its surface and contacting the cell or cell membrane preparation with a compound in the presence of a labelled form of an orexin-1 receptor ligand. The ligand may contain a radioactive label. The amount of labelled ligand bound to the receptors is measured, e.g. by measuring radioactivity.

Yet another screening technique involves the use of FLIPR equipment for high throughput screening of test compounds that inhibit mobilisation of intracellular calcium ions, or other ions, by affecting the interaction of an orexin-1 receptor ligand with the orexin-1 receptor.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention. The Descriptions D1-D11 illustrate the preparation of intermediates to compounds of the invention.

Abbreviation used herein are as follow:

HATU means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate

Description 1: (RS) 3-Carboxymethyl-4-{1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-piperazine-1-carboxylic acid *tert*-butyl ester

3-Methoxycarbonylmethylpiperazine-1-carboxylic acid *tert*-butyl ester (0.900g), HATU (1.396g), diisopropylethylamine (1.95 ml) and 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid (1.06g) were dissolved in dry dimethylformamide (10ml) and stirred at room temperature for 16 h. The solvent was then evaporated and the residue partitioned between dichloromethane and brine. The organic layer was dried ($MgSO_4$), evaporated to provide 4-{1-[5-(4-fluoro-phenyl)-2-methylthiazol-4-yl]-methanoyl}-3-methoxycarbonylmethyl piperazine-1-carboxylic acid *tert*-butyl ester as an amorphous solid (1.57g). Mass spectrum (API^+): Found 422 $[(M-C_4H_8)H^+]$. $C_{23}H_{28}FN_3O_5S$ requires 477.

This ester was dissolved in tetrahydrofuran (9ml) and 1*N* sodium hydroxide solution (9ml) and stirred at room temperature for 3 h. The solution was then diluted with ethyl acetate and acidified with 1*N* hydrochloric acid. The organic solution was washed with brine, dried ($MgSO_4$) and evaporated to yield the title compound as a colourless oil (1.58g). Mass spectrum (API^-): Found 462 $[(M-H)^-]$. $C_{22}H_{26}FN_3O_5S$ requires 463.

Description 2: (RS) 3-Aminomethyl-4-{1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-piperazine-1-carboxylic acid *tert*-butyl ester

D1 (0.500g) was dissolved in dry dichloromethane (20ml) and cooled to –20°C under an atmosphere of argon. Diphenylphosphinic chloride (0.256g) and diisopropylethylamine (0.184ml) were added to the stirred solution and stirring was continued at –20°C for 1 h. A solution of tetramethylguanidinium azide (0.171g) in acetonitrile (5ml) was then added and the solution stirred at 0°C for 2 h. The reaction was then partitioned between dichloromethane and water, and the organic solution washed with sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The resulting acid azide was dissolved in dry toluene (100ml) and heated at 90°C for 1 h. The solvent was then evaporated to yield the crude isocyanate, which was dissolved in dry tetrahydrofuran and stirred at room temperature for 16 h. with p-toluenesulphonic acid monohydrate (0.192g). The reaction was then evaporated and partitioned between dichloromethane and sodium bicarbonate

solution. The organic solution was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with a gradient of 0 to 10% [9:1 methanol-conc. ammonia solution] in dichloromethane. The title compound was obtained as a white amorphous solid (0.072g). Mass spectrum (API^+): Found 435 (MH^+). $C_{21}H_{27}FN_4O_3S$ requires 434.

Description 3: (RS) 3-[(5-Cyano-pyridin-2-ylamino)-methyl]-4-{1-[5-(4-fluoro-phenyl)-2-methylthiazol-4-yl]-methanoyl}-piperazine-1-carboxylic acid *tert*-butyl ester

D2 (0.072g) and 2-chloro-5-cyanopyridine (0.023g) were heated to 100°C in dimethylformamide (1ml) in the presence of diisopropylethylamine (0.028ml) for 24 h. under an atmosphere of argon. After cooling, the reaction mixture was partitioned between ethyl acetate and water. The organic solution was dried ($MgSO_4$) and evaporated. Chromatography on silica gel, eluting with a gradient of 0 to 10% methanol in ethyl acetate provided the title compound as a colourless gum (0.023g). Mass spectrum (API^+): Found 537 (MH^+). $C_{27}H_{29}FN_6O_3S$ requires 536.

Description 4: (RS)-4-Benzyl-3-carbamoyl-piperazine-1-carboxylic acid *tert*-butyl ester

A solution of (RS)-3-carbamoyl-piperazine-1-carboxylic acid *tert*-butyl ester [Bruce *et al.* Syn. Comm. 1995, 2673-84] (25g) and benzaldehyde (11.1ml) in 1,2-dichloroethane (550ml) was stirred at room temperature for 1.5h. Sodium triacetoxyborohydride (34.7g) was added in one portion and the resultant stirred for a further 18h. Dichloromethane (400 ml) was added and the mixture washed with saturated sodium hydrogen carbonate (600 ml). The organic layer was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 10 - 70 % ethyl acetate in hexane to afford the title compound as a colourless solid (32.4g). ^1H NMR ($CDCl_3$) δ: 1.45 (9H, s), 2.15 (1H, dt), 2.75 - 3.15 (4H, m), 3.28 (1H, d, J = 14 Hz), 3.85 (1H, broad d), 3.96 (1H, d, J = 14 Hz), 4.15 (1H, broad m), 5.63 (1H, broad s), 6.70 (1H, broad s), 7.2 - 7.5 (5H, m).

Description 5: (RS)-*C*-(1-Benzyl-4-methyl-piperazin-2-yl)-methylamine

1M Lithium aluminium hydride in tetrahydrofuran (112 ml) was added dropwise to a stirred solution of D4 (15 g) in anhydrous tetrahydrofuran (300 ml) at room temperature under argon. On complete addition the reaction mixture was stirred at room temperature for 0.5 h, then at reflux for a further 1.5 h. The mixture was cooled to room temperature and treated sequentially with water (19.5 ml), 2N sodium hydroxide (22.5 ml) and water (19.5 ml) dropwise. Sodium sulphate was added and the resultant stirred for 0.3h., filtered and the filtrate evaporated *in vacuo* to give the title compound (10.3 g). Mass spectrum (API^+): Found 220 (MH^+). $C_{13}H_{21}N_3$ requires 219.

Description 6: (RS)-*N*-(1-Benzyl-4-methyl-piperazin-2-ylmethyl)-2,2,2-trifluoro-acetamide

Trifluoroacetic anhydride (8.05 ml) in anhydrous dichloromethane (10ml) was added dropwise to a stirred solution of D5 (10.3 g) and triethylamine (9.25 ml) in anhydrous dichloromethane (400 ml) at 0°C under argon. The resultant was stirred at 0°C for 1h., then at room temperature for 18h. The mixture was washed with saturated sodium hydrogen carbonate (400 ml) and the organic layer dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with 50% ethyl acetate in hexane, then 0-10% methanol in ethyl acetate to yield the title compound as a pale green gum (6.06g). Mass spectrum (API^+): Found 316 (MH^+). $C_{15}H_{20}F_3N_3O$ requires 315.

Description 7: (RS)-2,2,2-Trifluoro-*N*-(4-methyl-piperazin-2-ylmethyl)-acetamide

A solution of D6 (6.06g) in ethanol (300 ml) was hydrogenated at atmospheric pressure in the presence of 10% palladium on charcoal (6g, 54% paste with water) for 18h. The mixture was filtered through Kieselguhr and the filtrate evaporated *in vacuo* to furnish the title compound as a colourless gum (4.07g). Mass spectrum (API^+): Found 226 (MH^+). $C_8H_{14}F_3N_3O$ requires 225.

Description 8. 4-Methyl-2-[(2,2,2-trifluoroethanoylamino)methyl]-piperazine-1-carboxylic acid *tert* butyl ester.

D7 (2.0g), di-*tert*-butyldicarbonate (2.33g) and triethylamine (1.47ml) were dissolved in dichloromethane (125ml) and stirred at room temperature for 16 h. The organic solution was then washed with water, brine and dried ($MgSO_4$). The solution was evaporated and the product chromatographed on silica gel eluting with 0 to 10% methanol in dichloromethane to provide the title compound as a white solid (2.60g). Mass spectrum (API^+): Found 326 (MH^+). $C_{13}H_{22}F_3N_3O_3$ requires 325.

Description 9. 2-Aminomethyl-4-methylpiperazine-1-carboxylic acid *tert* butyl ester

D8 (2.60g) was dissolved in methanol (100ml) and water (20ml) and stirred at room temperature for 3 days with potassium carbonate (2.2g). The solution was then evaporated to dryness and the residue digested in methanol. The suspension was filtered and the filtrate evaporated and redissolved in dichloromathane. This solution was dried ($MgSO_4$) and evaporated to yield the crude product, which was chromatographed on silica gel. Elution with a gradient of 0 to 10% [9:1 methanol/conc. ammonia solution] in dichloromethane provided the title compound as a colourless oil (1.77g). Mass spectrum (API^+): Found 230 (MH^+). $C_{11}H_{23}N_3O_2$ requires 229.

Description 10. 2-[(6,7-Difluoroquinoxalin-2-ylamino)methyl]-4-methylpiperazine-1-carboxylic acid *tert* butyl ester

D9 (0.80g) and 2-chloro-6,7-difluoroquinoxaline (0.70g) were dissolved in dimethylformamide (2ml) and heated at 100 °C for 12 h. After cooling, the reaction mixture was partitioned between ethyl acetate and sodium bicarbonate solution. The organic solution was then washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with a gradient of 0 to 10% [9:1 methanol/conc. ammonia solution] in dichloromethane. The title compound was obtained as a white amorphous solid (0.31g). Mass spectrum (API^+): Found 394 (MH^+). $C_{19}H_{25}F_2N_5O_2$ requires 393.

Description 11. (6,7-Difluoroquinoxalin-2-yl)-(4-methylpiperazin-2-ylmethyl)-amine

D10 (0.30g) was dissolved in trifluoroacetic acid (20ml) and stirred at room temperature for 3 h. The solution was then evaporated and the residue chromatographed on silica gel. Elution with a gradient of 0 to 10% [9:1 methanol/conc. ammonia solution] in dichloromethane provided the title compound as a white solid (0.22g). Mass spectrum (API^+): Found 294 (MH^+). $C_{14}H_{17}F_2N_5$ requires 293.

Example 1: (RS) 6-[(1-{1-[5-(4-Fluorophenyl)-2-methylthiazol-4-yl]-methanoyl}-piperazin-2-ylmethyl)-amino]-nicotinonitrile

D3 (0.022g) was dissolved in trifluoroacetic acid (3ml) and stirred at room temperature for 1h. The solution was then evaporated and the residue chromatographed on silica gel, eluting with a gradient of 0 to 10% [9:1 methanol-conc. ammonia solution] in dichloromethane. The title compound was obtained as a colourless gum (0.016g). Mass spectrum (API^+): Found 437 (MH^+). $C_{22}H_{21}FN_6OS$ requires 436.

Example 2. 1-{2-[(6,7-Difluoroquinoxalin-2-ylamino)-methyl]-4-methyl-piperazin-1-yl}-1-[5-(4-fluorophenyl)-2-methylthiazol-4-yl]-methanone

D11 (0.10g) was dissolved in dry dimethylformamide (2ml) and HATU (0.136g), diisopropylethylamine (0.190ml) and 5-(4-fluorophenyl)-2-methylthiazole-4-carboxylic acid (0.103g) added and the mixture shaken for 16 h. The reaction solution was then partitioned between ethyl acetate and water. The organic solution was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel, eluting with a gradient of 0 to 10% [9:1 methanol/conc. ammonia solution] in dichloromethane. The title compound was obtained as a white solid (0.12g). Mass spectrum (API^+): Found 513 (MH^+). $C_{25}H_{23}F_3N_6OS$ requires 512.

Example 3. 1-{2-[(6,7-Difluoroquinoxalin-2-ylamino)-methyl]-4-methyl-piperazin-1-yl}-1-[4-(4-fluorophenyl)-1-methyl-1*H*-pyrazol-3-yl]-methanone

The title compound was obtained as a white solid (0.154g) from D11 (0.10g) and 4-(4-fluorophenyl)-1-methyl-1*H*-pyrazole-3-carboxylic acid (0.097g) using the method of Example 2. Mass spectrum (API^+): Found 496 (MH^+). $C_{25}H_{24}F_3N_7O$ requires 495.

It is to be understood that the present invention covers all combinations of particular and preferred subgroups described herein above.

Determination of Orexin-1 Receptor Antagonist Activity

The orexin-1 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

HEK293 cells expressing the human orexin-1 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37°C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 3.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 90 min at 37°C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the cell plates gently shaken and incubated at 37°C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument and maintained at 37°C in humidified air. Prior to drug addition a single image of the cell plate was

taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

$K_b = IC_{50}/(1+([3/EC_{50}])$

where EC_{50} was the potency of human orexin-A determined in the assay (in nM terms) and IC_{50} is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values 6.4 to 7.4 at the human cloned orexin-1 receptor.

The orexin-2 receptor antagonist activity of the compounds of formula (I) was determined in accordance with the following experimental method.

Experimental Method

CHO-DG44 cells expressing the human orexin-2 receptor were grown in cell medium (MEM medium with Earl's salts) containing 2 mM L-Glutamine, 0.4 mg/mL G418 Sulphate from GIBCO BRL and 10% heat inactivated fetal calf serum from Gibco BRL. The cells were seeded at 20,000 cells/100 µl/well into 96-well black clear bottom sterile plates from Costar which had been pre-coated with 10 µg/well of poly-L-lysine from SIGMA. The seeded plates were incubated overnight at 37C in 5% CO_2.

Agonists were prepared as 1 mM stocks in water:DMSO (1:1). EC_{50} values (the concentration required to produce 50% maximal response) were estimated using 11x half log unit dilutions (Biomek 2000, Beckman) in Tyrode's buffer containing probenecid (10 mM HEPES with 145mM NaCl, 10mM glucose, 2.5 mM KCl, 1.5 mM $CaCl_2$, 1.2 mM $MgCl_2$ and 2.5mM probenecid; pH7.4). Antagonists were prepared as 10 mM stocks in DMSO (100%). Antagonist IC_{50} values (the concentration of compound needed to inhibit 50% of the agonist response) were determined against 10.0 nM human orexin-A using 11x half log unit dilutions in Tyrode's buffer containing 10% DMSO and probenecid.

On the day of assay 50 µl of cell medium containing probenecid (Sigma) and Fluo3AM (Texas Fluorescence Laboratories) was added (Quadra, Tomtec) to each well to give final concentrations of 2.5 mM and 4 µM, respectively. The 96-well plates were incubated for 60 min at 37C in 5% CO_2. The loading solution containing dye was then aspirated and cells were washed with 4x150 µl Tyrode's buffer containing probenecid and 0.1% gelatin (Denley Cell Wash). The volume of buffer left in each well was 125 µl. Antagonist or buffer (25 µl) was added (Quadra) the

cell plates gently shaken and incubated at 37C in 5% CO_2 for 30 min. Cell plates were then transferred to the Fluorescent Imaging Plate Reader (FLIPR, Molecular Devices) instrument. Prior to drug addition a single image of the cell plate was taken (signal test), to evaluate dye loading consistency. The run protocol used 60 images taken at 1 second intervals followed by a further 24 images at 5 second intervals. Agonists were added (by the FLIPR) after 20 sec (during continuous reading). From each well, peak fluorescence was determined over the whole assay period and the mean of readings 1-19 inclusive was subtracted from this figure. The peak increase in fluorescence was plotted against compound concentration and iteratively curve fitted using a four parameter logistic fit (as described by Bowen and Jerman, *TiPS*, 1995, **16**, 413-417) to generate a concentration effect value. Antagonist Kb values were calculated using the equation:

Kb= IC50/(1+([3/EC50])

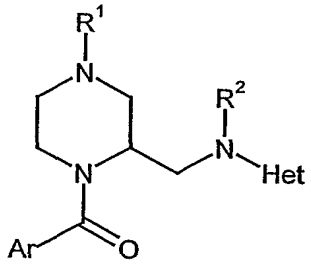
where EC50 was the potency of human orexin-A determined in the assay (in nM terms) and IC50 is expressed in molar terms.

Compounds of Examples tested according to this method had pKb values in the range <6.6 to 7.4 at the human cloned orexin-2 receptor.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation the following claims:

CLAIMS

1. A compound of formula (I):



(I)

wherein:

R^1 and R^2 independently represent hydrogen or optionally substituted (C_{1-6})alkyl;

Het represents an optionally substituted 5- or 6- membered heteroaryl group containing up to 3 heteroatoms selected from N, O, and S, or an optionally substituted bicyclic heteroaryl group containing up to 3 heteroatoms selected from N, O and S;

Ar represents a phenyl or a 5- or 6-membered heteroaryl group containing up to 3 heteroatoms selected from N, O and S, wherein the phenyl or heteroaryl group is substituted by R^3, and further optional substituents; or Ar represents an optionally substituted bicyclic aromatic or heteroaromatic group containing up to 3 heteroatoms selected from N, O and S;

R^3 independently represents hydrogen, an optionally substituted (C_{1-4})alkoxy, halo, optionally substituted (C_{1-6})alkyl, optionally substituted phenyl, or an optionally substituted 5- or 6-membered heterocyclic ring containing up to 3 heteroatoms selected from N, O and S;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein Het represents pyridyl, pyrimidinyl or quinoxalinyl.

3. A compound according to claim 1 or 2 wherein Ar represents an optionally substituted thiazolyl or pyrazolyl.

4. A compound according to any one of claims 1 to 3 wherein R^3 represents an optionally substituted phenyl.

5. The compound of any one of Examples 1 t

6. A pharmaceutical composition comprising a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

7. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

Intern pplication No
PCT/GB 02/05676

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/14 C07D403/14 C07D401/14 A61K31/497 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 343 900 A (GLAXO) 29 November 1989 (1989-11-29) page 1 -page 6; claims	1,6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 March 2003	11/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Francois, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 02/05676

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Interna ..plication No
PCT/GB 02/05676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 343900 A	29-11-1989	AU 625192 B2	02-07-1992
		AU 3511989 A	14-12-1989
		DK 247789 A	24-11-1989
		EP 0343900 A2	29-11-1989
		FI 892468 A	24-11-1989
		JP 2056470 A	26-02-1990
		NZ 229239 A	25-06-1991
		PT 90619 A ,B	30-11-1989
		US 4943578 A	24-07-1990
		ZA 8903874 A	25-04-1990